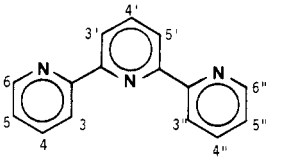
Table I. 300-MHz ^{1}H NMR Data for *N*-Oxides of 2,2′:6′,2″-Terpyridine



	3	4	5	6	3′	4′	5′	3″	4″	5″	6″
terpyridine	8.62	7.82	7.33	8.70	8.46	7.96	8.46	8.62	7.86	7.33	8.70
mono-*N*-oxide 1	8.34	~7.32	~7.32	8.34	9.00	7.95	8.47	8.47	7.81	~7.32	8.68
di-*N*-oxide 2	8.20	~7.35	~7.35	8.35	8.94	7.98	8.94	8.20	~7.35	7.35	8.35
tri-*N*-oxide 3	←	7.95–7.74	→	8.48	←		7.95–7.74	→			8.48

chemical shifts are reported in parts per million downfield from Me_4Si. Infrared spectra were obtained on a Beckman IR-4250 spectrometer. Ultraviolet spectra were obtained on a Perkin-Elmer 330 spectrometer. Mass spectra were obtained by direct sample introduction into a Hewlett-Packard 5933A GC–mass spectrometer or by introduction as a 0.1 M NH_4OAc solution into a Biospec LC–MS with a thermospray ionization interface. High-resolution mass spectral analyses were carried out on a Kratos MS-50TA Spectrometer at the Chemistry Department, Texas A&M University. All solvents were freshly distilled reagent grade.

2,2′:6′,2″-Terpyridine Mono-*N*-oxide (1). To 0.47 g (2 mmol) of 2,2′:6′,2″-terpyridine in 20 mL of CH_2Cl_2 was added a solution of 0.40 g (2 mmol) of 85% *m*-chloroperbenzoic acid in 20 mL of CH_2Cl_2, and the mixture was allowed to stir at room temperature for 13 h.[3] After washing with 5% Na_2CO_3 solution and drying over anhydrous $MgSO_4$, the solvent was evaporated to give 0.38 g of solid, which was chromatographed on 15 g of alumina, eluting with CH_2Cl_2 followed by EtOAc. The early fractions of CH_2Cl_2 gave 0.04 g of unreacted terpyridine, while later fractions gave 0.20 g (40%) of mono-*N*-oxide 1, mp 134–135 °C. The early EtOAc fractions gave 0.11 g of 2,2′:6′,2″-terpyridine 1,1″-di-N-oxide (2), mp 230–231 °C. The mono-*N*-oxide was characterized by its spectral properties: IR (KBr) 1582, 1568, 1430, 1255, 1104, 905, 868, 763, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (d, $H_{3'}$, J = 8 Hz), 8.68 (d, $H_{6''}$, J = 4.8 Hz), 8.47 (overlapping d, $H_{5'}$ and $H_{3''}$, J = 8 Hz), 8.34 (overlapping d, H_3 and H_6), 7.95 (t, $H_{4'}$, J = 8 Hz), 7.81 (t, $H_{4''}$), 7.40–7.23 (m, H_4, H_5, and $H_{5''}$); UV λ_{max} (95% EtOH) (ϵ) 305 (10 100), 275 (13 900), 225 (26 100), 207 (24 600); mass spectrum, m/z (relative intensity) 250 (M + 1, 17), 249 (M, 82), 233 (M − 16, 18), 221 (58), 117 (100), 78 (86). Anal. Calcd for $C_{15}H_{11}N_3O$: m/z 249.0902. Found: m/z 249.0901.

2,2′:6′,2″-Terpyridine 1,1″-Di-*N*-oxide (2). The procedure described above for 1 was followed using 0.47 g (2 mmol) of 2,2′,2″-terpyridine and 1.30 g (7.5 mmol) of *m*-chloroperbenzoic acid to yield 0.44 g (83%) of 2,2′:6′,2″-terpyridine 1,1″-di-*N*-oxide, which was purified by washing with acetone, mp 232–233 °C: IR (KBr) 3070, 1560, 1486, 1453, 1425, 1261, 1102, 900, 765 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (d, $H_{3'}$ and $H_{5'}$, J = 8 Hz), 8.35 (d, H_6 and $H_{6''}$, J = 6.2 Hz), 8.20 (d, H_3 and $H_{3''}$, J = 8.2 Hz), 7.98 (t, $H_{4'}$, J = 8 Hz), 7.41–7.27 (m, H_4, H_5, $H_{4''}$, and $H_{5''}$); UV λ_{max} (95% EtOH) (ϵ) 235 (13 000), 204 (36 100); mass spectrum, m/z (relative intensity) 266 (M + 1, 5), 265 (M, 28), 249 (M − 16, 15), 233 (M − 32, 16), 220 (21), 105 (45), 78 (100). Anal. Calcd for $C_{15}H_{11}N_3O_2$: m/z 265.0851. Found: m/z 265.0849.

2,2′:6′,2″-Terpyridine Tri-*N*-oxide (3). A solution of 0.4 g (1.7 mmol) of 2,2′,2″-terpyridine in 2.0 mL of glacial acetic acid and 1.5 mL of 30% hydrogen peroxide was heated for 2 h at 80 °C. After addition of a further 1.5 mL of 30% hydrogen peroxide, the temperature was raised to 90 °C and maintained there for 18 h. The mixture was poured into 20 mL of acetone, and after standing for several hours, the precipitate was collected and washed with acetone to give 0.35 g (73%) of tri-*N*-oxide 3, mp 320 °C dec (lit.[1] mp 321–322 °C); IR (KBr) 1470, 1424, 1390, 1245, 1110, 905, 863, 790, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, H_6 and $H_{6''}$, J = 6.5 Hz), 7.95–7.74 (overlapping m, 9 H); mass spectrum, m/z (relative intensity) 282 (M + 1, 3), 281 (M, 10), 264 (M − 16, 6), 249 (M − 32, 2), 233 (M − 48, 5), 220 (4), 150 (20), 104 (33), 78 (100).

(3) Craig, J. C.; Purushothaman, K. K. *J. Org. Chem.* **1970**, *35*, 1721.

5,6-Dihydro-7,8-benzoquinoline *N*-Oxide (5a). The procedure described above for 1 was followed using 0.20 g (1.1 mmol) of 5,6-dihydro-7,8-benzoquinoline (**4a**)[4] and 0.21 g (1.2 mmol) of *m*-chloroperbenzoic acid to yield 0.12 g (55%) of **5a** as a white solid, mp 42–43 °C: IR (thin film) 2940, 2840, 1680, 1472, 1445, 1420, 1300, 1250, 1227, 1008, 790 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 9.38 (dd, H_{10}, J = 3.9, 5.0 Hz), 8.21 (dd, H_2, J = 2.4, 5.4 Hz), 7.41–7.20 (m, 3 H, Ar H), 7.09–7.02 (m, 2 H, Ar H), 2.84 (s, 4 H, CH_2CH_2). Anal. Calcd for $C_{13}H_{11}NO$: m/z 197.0841. Found: m/z 197.0854.

3,2′-Trimethylene-2-phenylpyridine *N*-Oxide (5b). The procedure described above for 1 was followed using 0.25 g (1.28 mmol) of 3,2′-trimethylene-2-phenylpyridine (**4b**)[5] and 0.40 g (2.32 mmol) of *m*-chloroperbenzoic acid to yield 0.14 g (35%) of **5b** as a semisolid: IR (KBr) 1580, 1530, 1420, 1390, 1192, 1069, 895, 753, 738 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 8.38 (dd, H_2, J = 3.0, 4.8 Hz), 7.98 (m, 1 H), 7.42–7.16 (m, 5 H, Ar H), 2.69–2.13 (m, 4 H, CH_2CH_2); ^{13}NMR (20 MHz, $CDCl_3$) δ 139.6, 139.2, 138.3, 131.8, 129.9, 129.6, 129.1, 128.1, 127.5, 125.4, 123.6, 32.0, 30.0 (2 overlapping peaks). Anal. Calcd for $C_{14}H_{13}NO$: m/z 211.0997. Found: m/z 211.1015.

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Registry No. 1, 97721-16-9; **2**, 97721-17-0; **3**, 78017-86-4; **4a**, 56568-10-6; **4b**, 97721-20-5; **5a**, 97721-18-1; **5b**, 97721-19-2; 2,2′:6′,2″-terpyridine, 1148-79-4.

(4) Koyama, J.; Sugita, T.; Suzuta, Y.; Irie, H. *Chem. Pharm. Bull.* **1983**, *31*, 2601.

(5) This material was prepared in the same manner as **4a**.[4] Complete details will be furnished in a future publication.

Synthesis of 2-*S*-Cysteinylhistidine and 2-Mercaptohistidine via Bromo Lactone Derivative of Histidine

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Aromatic amino acids may be found in nature combined covalently with cysteine through a thioether bond. 2-*S*-Cysteinyltryptophan (tryptathionine) and its derivatives are constituents of toxic peptides from fungus *Amanita phalloides*.[1] Savige and Fontana[2] have reported a syn-

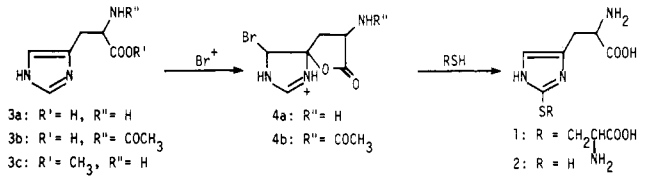
(1) Whieland, Th. In "Progress in the Chemistry of Organic Natural Compounds"; Zechmeister, L. Z., Ed.; Springer-Verlag: New York, 1967; Vol. 25, pp 214–250.

0022-3263/85/1950-3636$01.50/0

thesis of tryptathionine by the reaction of cysteine with a peracetic acid oxidation product of tryptophan. 5-*S*-Cysteinyl-3,4-dihydroxyphenylalanine (5-*S*-cysteinyl-DOPA) is present in the urine of melanoma patients at a high level[3] and in normal subjects at a low level. 2-*S*-Cysteinyl-DOPA and 2,5-*S*,*S*′-dicysteinyl-DOPA have also been detected in the urine.[4] These thioether derivatives of DOPA are formed by the nucleophilic addition of cysteine to dopaquinone produced by the action of tyrosinase.[5]

Studies on the biosynthesis of ergothioneine in *Neurospora crassa* demonstrated that this 2-mercaptohistidine betaine is formed through the condensation of cysteine with the imidazole ring of histidine betaine.[6] More recently, Lerch[7] has shown that a tyrosinase from *Neurospora crassa* contains a peptide sequence Cys-Thr-His in which the cysteinyl residue is covalently linked via a thioether bridge to the histidyl residue at C-2 of the imidazole ring.

In the studies on the reaction of bromine with imidazoles, Schmir and Cohen[8] have found that a labile bromo lactone is formed as an intermediate in the oxidation of imidazole-4-propionic acid (and its analogues). The present paper describes that the bromo lactone formed in situ from histidine reacts readily with cysteine to form 2-[(2-amino-2-carboxyethyl)thio]histidine (2-*S*-cysteinyl-



histidine; **1**). The thioether is converted to 2-mercaptohistidine (**2**) by hydrolysis with HI. 2-Mercaptohistidine is also prepared directly by the reaction of the bromo lactone with Na_2S. In the course of this study, a simple method was found for the preparation of 5-bromohistidine, a hitherto unknown amino acid.

Results and Discussion

Histidine (**3a**) reacted rapidly with 1 equiv of bromine to give a colorless intermediate which, by analogy with the results of Schmir and Cohen,[8] is likely to have the bromo lactone structure **4a**. Addition of cysteine to a solution of the bromo intermediate afforded a new Pauli positive compound. The compound could be obtained in a crystalline form in 19% yield after chromatography on Dowex 50W. NMR analysis of the compound revealed the presence of two alanyl residues and the lack of the C-2 hydrogen of imidazole ring. These data, coupled with the elemental composition, indicate that the compound is 2-*S*-cysteinylhistidine (**1**). Evidence for the site of S-substitution on the imidazole ring was provided by conversion of **1** to 2-mercaptohistidine (**2**) by hydrolysis with HI (see below).

To prove that the bromo lactone **4a** is indeed the reactive intermediate, *N*-acetylhistidine **3b** and histidine methyl ester (**3c**) were subjected to the bromination followed by the reaction with cysteine. The compound **3b**, which possesses a free carboxyl group, gave a similar yield of **1** after removal of the acetyl group by hydrolysis. Thus a bromo lactone intermediate **4b** may be formed by the reaction of **3b** with bromine. On the other hand, the compound **3c**, which lacks a free carboxyl group, afforded only a trace amount of **1**, and moreover, acid hydrolysis did not increase the yield of **1**. These findings suggest that the carboxyl group but not the amino group in the alanyl residue participates in the formation of a reactive intermediate. A major product of the reaction of **3c** with bromine was assumed to be a bromohistidine methyl ester. A bromohistidine was obtained after acid hydrolysis in 39% yield. The substitution of bromine was established to be at C-5 on the basis of a NMR spectrum which revealed the presence of a signal for the C-2 hydrogen at δ 8.86; under the same conditions, a NMR spectrum of 5-iodohistidine[9] exhibited a singal for the C-2 hydrogen at δ 8.90.

2-*S*-Cysteinylhistidine (**1**) was next examined for hydrolytic conversion to 2-mercaptohistidine (**2**). Hydrolysis of **1** in 6 M HCl gave a complex mixture of products. However, the conversion was successfully achieved by refluxing in 57% HI for 16 h. Major products were found to be 2-mercaptohistidine (**2**) and alanine, which were separated by chromatography on Dowex 50W and crystallized. The structure **2** was proved by the direct comparison of IR, UV, and NMR spectra with those of a commercial sample as well as by elemental analysis. Although the product **2** retained most of its optical purity, alanine, derived from the cysteinyl moiety, was racemic. This fact suggests that the reaction may proceed via elimination of **2** to form dehydroalanine followed by reduction of the latter with HI to form racemic alanine.

2-Mercaptohistidine (**2**) was more readily prepared by the reaction of the bromo lactone **4a** with Na_2S. The compound was obtained in 12% yield after chromatography on Dowex 50W.

The present study have shown that the bromo lactone **4a**, formed by the reaction of histidine with bromine, reacts smoothly with cysteine to form 2-*S*-cysteinylhistidine (**1**). This is the first report for the synthesis of this thioether amino acid. This study also describes a single-step synthesis of 2-mercaptohistidine (**2**) by the reaction of the bromo lactone with Na_2S. Previous methods for the synthesis of **2** required several steps.[10]

Experimental Section

2-Mercapto-(*S*)-L-histidine, purchased from ICN Pharmaceutical, Inc., Cleveland, OH, was purified by recrystallization from H_2O–EtOH in the presence of dithiothreitol. 5-Iodo-(*S*)-L-histidine was prepared according to Brunings.[9]

UV spectra were recorded on a Beckman Model UV 5260 spectrophotometer, and optical rotations were measured with a JASCO DIP-181 digital polarimeter at 25 °C. ^1H NMR spectra were taken with a JEOL-PMX 60 spectrophotometer using as an internal reference the methyl signal of 2-methyl-2-propanol, which appeared at δ 1.28. Amino acid analyses were carried out on a JEOL JLC-6AH amino acid analyzer using a buffer system of four lithium citrate buffers. Microanalyses were performed in the Microanalytical Laboratory, Faculty of Science, Osaka University. For TLC analyses, precoated cellulose plates were used in a solvent system of 3:1 (v/v) 1-propanol-1 M HCl. Dowex 50W-X2, 200–400 mesh, was used for ion-exchange chromatography.

Preparation of 2-*S*-(*S*)-Cysteinyl-(*S*)-histidine (1). To a stirred, ice-cooled solution of (*S*)-L-histidine·HCl·H_2O (2.09 g,

(2) Savige, W. E.; Fontana, A. *Int. J. Peptide Protein Res.* **1980**, *15*, 102–112.
(3) Agrup, G.; Agrup, P.; Andersson, T.; Hafström, L.; Hansson, C.; Jacobsson, S.; Jönsson, P.-E.; Rorsman, H.; Rosengren, A.-M.; Rosengren, E. *Acta Derm-Venereol.* **1979**, *59*, 381–388.
(4) Prota, G.; Rorsman, H.; Rosengren, A.-M.; Rosengren, E. *Experientia* **1978**, *33*, 720–721.
(5) Ito, S.; Prota, G. *Experientia* **1977**, *33*, 1118–1119.
(6) Ishikawa, Y.; Israel, S. E.; Melville, D. B. *J. Biol. Chem.* **1974**, *249*, 4420–4427.
(7) Lerch, K. *J. Biol. Chem.* **1982**, *257*, 6414–6419.
(8) Schmir, G. L.; Cohen, L. A. *Biochemistry* **1965**, *4*, 533–538.
(9) Brunings, K. L. *J. Am. Chem. Soc.* **1947**, *69*, 205–208.
(10) Ashley, J. N.; Harrington, C. R. *J. Chem. Soc.* **1930**, 2586–2590.

10 mmol) in H_2O (100 mL) was added bromine (510 μL, 10 mmol) in one portion. After ca. 7 min, when the yellow color of bromine disappeared, (*S*)-L-cysteine (1.21 g, 10 mmol) was added to the solution. The resulting mixture was kept in the ice–water bath for 2 h and then passed through a column (2.0 × 10 cm) of Dowex 50W (H^+ form, equilibrated with H_2O). The components in the mixture were eluted with 1 M HCl and fractions of 100 mL were collected and analyzed by TLC. Fractions 2–5 that contained 2-*S*-cysteinylhistidine (1) were combined, and the solvent was removed to dryness in a rotary evaporator. The residue was applied on a column (2.0 × 6.5 cm) of Dowex 50W (equilibrated with 2 M HCl) and eluted with 2 M HCl (20 mL/fraction). Fractions 3–8 that contained **1** were evaporated to afford the 3 HCl salt of **1** (1.04 g). The amino acid was further purified in the free form by two crystallizations from H_2O (adjusted to pH 6 with pyridine–EtOH: colorless crystals (540 mg, 19% yield); mp >280 °C; $[\alpha]_D$ +147° (5 mg/mL, 1 M HCl); UV (0.1 M HCl) λ_{max} (ϵ) 253 nm (7610), 219 (5270); ^1H NMR (2 M DCl–D_2O) δ 3.52 (2 H, d, J = 7 Hz, Ar CH_2), 3.86 (2 H, d, J = 5 Hz, SCH_2), 4.52 (1 H, t, J = 7 Hz, CH), 4.60 (1 H, t, J = 5 Hz, CH), 7.59 (1 H, s, Ar H); amino acid analysis, 362 min (γ-aminobutyric acid; 356 min). Anal. Calcd for $C_9H_{14}N_4O_4S{\cdot}0.5H_2O$: C, 38.16; H, 5.34; N, 19.78; S, 11.32. Found: C, 38.31; H, 5.22; N, 19.75; S, 11.29.

Preparation of 2-Mercapto-(*S*)-histidine (2) by HI Hydrolysis of 2-*S*-Cysteinylhistidine (1). A mixture of 2-*S*-cysteinylhistidine (**1**; 300 mg, 0.106 mmol) and red P (1.5 g) in 57% HI (10 mL) was heated under reflux. After 16 h when the reaction completed by 98% (by amino acid analysis), the mixture was evaporated to dryness at 70 °C, and the residue, taken up in H_2O, was passed through a column (2.0 × 7.5 cm) of Dowex 50W (H^+ form, equilibrated with H_2O). The components in the mixture were eluted with H_2O (50 mL) and then with 1 M HCl. The first 100 mL of the HCl eluate that contained alanine and 2-mercaptohistidine (**2**) was evaporated to dryness, and the residue was applied on a column (2.0 × 23 cm) of Dowex 50W (equilibrated with 0.15 M HCl; 20-mL fractions being collected and analyzed by UV and TLC). Fractions 24–33 and 30–39 contained alanine and **2**, respectively. Evaporation of fractions 24–30 and 31–39 afforded the HCl salt of alanine (130 mg) and 2HCl salt of **2** (209 mg). Further purification of **2** as the free amino acid was achieved by crystallization from H_2O (adjusted to pH 6 with pyridine)–EtOH in the presence of dithiothreitol: colorless crystals (126 mg, 62% yield); mp >280 °C; $[\alpha]_D$ −9.8° (5 mg/mL, 1 M HCl); UV (0.1 M HCl) λ_{max} (ϵ) 257 nm (16300); ^1H NMR (2 M DCl–D_2O) δ 3.35 (2 H, d, J = 7 Hz, CH_2), 4.47 (1 H, t, J = 7 Hz, CH), 7.02 (1 H, s, Ar H); amino acid analysis, 104 min (aspartic acid, 96 min). Anal. Calcd for $C_6H_9N_3O_2S$: C, 38.49; H, 4.85; N, 22.44; S, 17.13. Found: C, 38.13; H, 4.88; N, 22.00; S, 16.85. A commercial sample of **2**: $[\alpha]_D$ −10.6° (5 mg/mL, 1 M HCl) (lit. $[\alpha]_D$ −9.5°);[10] UV (0.1 M HCl) λ_{max} (ϵ) 257 nm (16000).

Free (*RS*)-alanine (51 mg, 54% yield) was obtained by crystallization from H_2O (adjusted to pH 6 with pyridine)–EtOH: $[\alpha]_D$ 0.0° (5 mg/mL, 1 M HCl).

Preparation of 2-Mercapto-(*S*)-histidine (2) by a Direct Method. To a stirred, ice-cooled solution of (*S*)-histidine·HCl·H_2O (1.05 g, 5 mmol) in H_2O (50 mL) was added bromine (255 μL, 5 mmol) in one portion. After ca. 7 min, $Na_2S{\cdot}9H_2O$ (1.20 g, 5 mmol) was added to the solution. The resulting mixture was kept in the ice–water bath for 2 h and then passed through a column (2.0 × 7.5 cm) of Dowex 50W (H^+ form, equilibrated with H_2O). The components in the mixture were eluted with H_2O (50 mL) and then with 1 M HCl. The first 50 mL of the HCl eluate that contained 2-mercaptohistidine (**2**) was evaporated to dryness, and the residue was applied on a column (2.0 × 20 cm) of Dowex 50W (equilibrated with 0.2 M HCl) and eluted with 0.2 M HCl (20 mL/fraction). Fractions 22–28 that contained **2** were evaporated to afford the 2HCl salt (197 mg). The amino acid was purified in the free form as described above: colorless crystals (108 mg, 12% yield); mp >280 °C; $[\alpha]_D$ −10.6° (5 mg/mL, 1 M HCl) λ_{max} (ϵ) 257 nm (17200). Found: C, 38.17; H, 4.91; N, 21.97; S, 16.82.

Preparation of 5-Bromo-(*S*)-histidine. To a stirred, ice-cooled solution of (*S*)-L-histidine methyl ester hydrochloride (1.03 g, 5 mmol) in H_2O (50 mL) was added bromine (305 μL, 6 mmol). After the disappearance of the yellow color, 6 M HCl (10 mL) was added and the mixture refluxed for 1 h to cleave the ester bond. The resulting dark violet solution was evaporated to dryness, and the residue was applied on a column (2.0 × 23 cm) of Dowex 50W (equilibrated with 1 M HCl) and eluted with 1 M HCl (20 mL/fraction). Fractions 30–54 that contained 5-bromohistidine were evaporated to afford the 2HCl salt (672 mg). The amino acid was purified in the free form by crystallization from H_2O (adjusted to pH 6 with pyridine)–acetone: colorless crystals (460 mg, 39% yield); mp 238 °C dec; $[\alpha]_D$ +11.1° (10 mg/mL, 1 M HCl); UV (0.1 M HCl) λ_{max} (ϵ) 220 nm (4970); ^1H NMR (2 M DCl–D_2O) δ 3.51 (2 H, d, J = 7 Hz, CH_2), 4.51 (1 H, t, J = 7 Hz, CH), 8.86 (1 H, s, Ar H); amino acid analysis, 356 min (γ-aminobutyric acid, 356 min). Anal. Calcd for $C_6H_8N_3O_2Br$: C, 30.79; H, 3.45; N, 17.96; Br, 34.14. Found: C, 31.13; H, 3.84; N, 17.96; Br, 34.03.

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Registry No. 1, 77504-36-0; **2**, 2002-22-4; **2**·2HCl, 97589-45-2; **4a**, 97486-07-2; (*S*)-L-histidine hydrochloride, 1007-42-7; (*R*)-L-cysteine, 52-90-4; (*S*)-L-histidine methyl ester hydrochloride, 22888-60-4; 5-bromo-(*S*)-histidine, 97486-06-1.

Electrophilic Benzylation and Nitration of 2,6-Dimethylanisole, 2,6-Dimethylphenol, and 2,6-Diisopropylphenol. Isomer Distribution and Mechanistic Considerations

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Aromatic benzylation reactions are among the most thoroughly investigated reactions in Friedel–Crafts chemistry both from the view point of synthetic usefulness and mechanistic importance.[1]

Olah and co-workers[2] reported a detailed investigation of electrophilic benzylation of benzene and toluene using a variety of Friedel–Crafts catalysts and discussed mechanistic aspects. Predomiment ortho–para substitution of toluene was observed. Similar studies were subsequently also carried out on anisole.[3]

Recently, Miller et al.[4] studied the benzylation of 2,6-dimethylphenol (2,6-DMP) and 2,6-dimethylanisole (2,6-DMA) with benzyl chloride using $ZnCl_2$ catalyst or with benzyl alcohol catalyzed by H_2SO_4. Predominent "meta" substitution was observed in reaction of 2,6-DMA (68–74% 3-substitution), whereas 2,6-DMP gave 38–41% of the 3-benzyl isomer. During the course of the study by Miller et al.[4] several possible mechanisms including intermolecular benzyl transfer (rearrangement), rearrangement within the σ-complex and ortho benzylation (ipso attack) followed by rearrangement could be excluded. But some evidence was presented to support partial intervention of a mechanism in which O-benzylation occurs followed by intermolecular benzyl shift. It was, however, concluded that the product of meta benzylation arises by direct attack.[4] Similar results were obtained on alkylation of 2,6-DMP with allyl alcohol using H_2SO_4 as catalyst or with allyl halides using $ZnCl_2$.[5]

An interesting kinetic study by Cerfontain et al.[6] on the aprotic (SO_3) and protic (H_2SO_4) sulfonation of several

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